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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,400	06/22/2005	Stanton L. Gerson	CWR-7784PCT/US	7253

68705 7590 07/07/2010

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EXAMINER	
PACKARD, BENJAMIN J	
ART UNIT	**PAPER NUMBER**
1612	
MAIL DATE	**DELIVERY MODE**
07/07/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,400	GERSON ET AL.	
	Examiner	Art Unit	
	Benjamin Packard	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,60,65,75,78,98,234 and 235* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,59-62,65,67,75,78,83,85,88,98,101,103-106,111,113,172 and 230-235.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,61,62,67,83,85,88,101,103-106,111,113,172 and 230-233.

DETAILED ACTION

Applicants' arguments, filed 04/07/2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 1st ¶ - New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59, 60, 65, 75, 78, 98, 234, and 235 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has amended claim 58 to recite "the AP endonuclease inhibitor comprising a small molecule compound ~~includes an~~ having a primary amine group that ~~and~~ binds to an aldehyde group of the AP site ~~to prevent~~ and prevents AP endonuclease-mediated cleavage of phosphodiester bonds." The amendment presents new matter as follows:

First, while the specification discloses a number of compounds at pg 19, no where does the specification make the correlation between the specifically disclosed

compounds and the now recited broader class of "small molecule" compounds. Such an extrapolation appears to have first been made in the response by Applicants filed 04/07/10 at pg 21 where the compounds disclosed are first described as “small molecule” compounds.

Second, the binding of the “primary” amine to an aldehyde group only appears to be disclosed at pg 53 lines 31-32 with regards to the reaction of the primary amine with the carbonyl group of the abasic site and its functional relationship to Compound A which was found to competitively bind to the aldehyde group of the AP site. Again, the disclosure does not suggest this mechanism was considered beyond the tested compound A as now claimed.

Third, the prevention of AP endonuclease-mediated cleavage of phosphodiester bonds based on the mechanism of the primary amine reacting with the aldehyde group of the AP site does not appear to be considered beyond compound A.

***Claim Rejections - 35 USC § 112 1st ¶* - Lack of Written Description**

Claims 59, 60, 65, 75, 78, 98, 234, and 235 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, previously rejecting the term “AP endonuclease inhibitors” and now rejecting "AP endonuclease inhibitor comprising a small molecule compound having a primary

amine group that binds to an aldehyde group of the AP site and prevents AP endonuclease-mediated cleavage of phosphodiester bonds".

Applicants assert the claim has been amended to recite that the AP endonuclease inhibitor is a small molecule compound that has a primary amine group and binds to an aldehyde group on the AP site to prevent AP endonuclease-mediated cleavage of phosphodiester bonds. Further, Applicants assert the skilled artisan would recognize that Applicants were in possession of AP endonuclease inhibitors as recited in the claims and the Office failed to establish a *prima facie* case that the specification does not satisfy the written description requirement. Applicants then review the disclose of the instant specification where certain specific species are disclosed at pg 18 lines 18+ and the functional effect where the primary amine is reactive site is disclosed at pg 18 lines 29+. Applicants then discuss the screening assay which may be used to identify new inhibitors of BER which have the ability to block AP site cleavage at pg 37 -39 and Example 14.

Examiner disagrees. First, Examiner notes the claimed “AP endonuclease inhibitor” appears now be limited to small molecule compounds, but such compounds are also now required to have a primary amine group that binds to an aldehyde group of the AP site and thereby prevents AP endonuclease-mediated cleavage of phosphodiester bonds. Note, Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement (see MPEP 2163). The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the

unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Suggitt and Bibby, (Clinical Cancer Research, Vol 11, 971-981, see PTO-892 dated 4/15/08), to reflect the level of art. Suggitt and Bibby teaches the unpredictability of treating cancer. Note however, that the current human tumor cell line in vitro screen is generally unpredictable. Modern methods are susceptible to false-positive and false-negative results. (page 973 1st paragraph on right-hand column). Difficulty in determining results leads to difficulty in testing for effectiveness of compounds, which leads to unpredictability in treating cancers. Further, where the method is directed to potentiating a therapeutic effect of anticancer agents, such unexpected results would be even more unpredictable in nature.

Second, a lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See MPEP 2163. While Applicant is correct that not all compounds need be disclosed, the question is whether a sufficient number of species are disclosed, when coupled with the functional disclosure, would allow the skilled artisan to immediately envisage the compounds within the scope of the claims. As Applicants have not made the correlation between the class of small molecule compounds generally and the primary amine functional group, as discussed above in the new matter rejection, the skilled artisan would not immediately know which primary amine containing small molecules would be able to provide the functional effect of preventing AP endonuclease-mediated cleavage of phosphodiester bonds. While Applicants do present an assay for testing the compounds, the ability to test in the

future is irrelevant to whether there is sufficient written description when filed, given the standard is not whether the skilled artisan would test compounds in the future for efficacy, but instead whether at the time of filing the skilled artisan would immediately envision the claimed compounds.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59, 60, 65, 75, 78, 98, and 234-241 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a method of potentiating a therapeutic effect of temozolamide by combination with methoxyamine (MX), does not reasonably provide enablement for treating the broader method of potentiating a therapeutic effect of anticancer agents which induce formation of AP sites by combination with base excision repair inhibitors.

Applicants assert there is sufficient direction or guidance disclosed to enable the skilled artisan to make and use the claimed methods using only routine experimentation. Specifically, Applicants assert the list of known agents which induce formation of AP sites at pg 22 of the instant specification are known in the art to treat various cancer and each specific cancer would be well known to one skilled in the art. Applicants then assert base excision repair inhibitors inhibit the mechanisms the cancer cells use to inhibit the cytotoxic function of the anticancer agents, where working

examples are presented in Examples 1, 4, 10, and 11. Finally, Applicant asserts a *prima facia* case was note made as the Examiner has not provided any factual evidence to doubt the objective truth of Applicants statements, where the Federal Circuit in the case In re Brana, 51 F.3d 1560 (Fed. Cir. 1995) held that working examples showing treatment of cancer in a mouse model were sufficient to support enablement.

Examiner disagrees. First, Examiner notes the instant claims are not directed simply to "treating" cancers, but to potentiating the effect of the anticancer agent. Thus, even if the skilled artisan knew what drugs were approved or known to be useful for specific cancer lines, the skilled artisan would be required to determine if the combination of agents would cause a potentiating effect when administered *in vivo*.

Second, with regards to *in vivo* expectation, direction in the specification is only one factor in determining scope of enablement. Here, while there are working examples which use methoxyamine in combination with various anticancer agents, the scope of showing for the AP endonuclease inhibitor appears to be limited to a single compound. There is discussion that O^6benzylguanin also potentiates the anti-tumor effect of methylating agents (pg 52 of instant spec), but such a disclosure is limited to a single anti-cancer agent. The ability to predictably extrapolate an expectation of success from these limited embodiments to the full scope of the claims is outweighed by the unpredictable nature of the art, as discussed in the Office Action mailed 4/15/08 where discussing Suggit and Bibby, Clinical Cancer Research, v11 (2005) 971-981, and incorporated herein by reference. Examiner notes the claims are not limited to treating cancers which have been approved or are known and thus include the potential for

treating cancers which are not known or approved. Where such is included in the method claims, such treatments are not enabled.

Finally, with regards to In re Brana, the claims at issue were directed to compound claims, not method claims. Where claims are directed to a compound, only one use need be provided for the compounds to be enabled. On the other hand, where claims are directed to a method of treatment, as the instant claims are, the specification must be enabled for the scope of the claims. As discussed above, such enablement is not provided by the instant specification.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 59, 60, 65, 75, 78, 98, 234-237, and 239-241 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fortini et al (Carcinogenesis vol. 13 no. 1 (1992) pp.87-93).

Applicants assert the disclosure does not enable in vivo results for treating cancer, given the instantly amended claims are directed to treating a patient where there is no evidence in fact or technical literature to show that an *in vitro* CHO assay is recognized by the skilled artisan was being a model for a cancer cell of a patient with cancer. Applicants then note at the time of filing the use of combinations of BER inhibitors with anticancer agents for the treatment of cancer in a patient was

unpredictable. Additionally, Applicants assert Fortini et al teaches away from administering a BER inhibitor to potentiate the cytotoxicity of an anticancer agent.

Examiner disagrees. First, the *in vitro* CHO assay appears to be acceptable for studying AP sites, and recognition of such a mechanistic effect would reasonably be expected to translate into *in vivo* activity. Such a position is acceptable in the art as evidenced by Rosa et al (Nucleic Acids Research, Vol. 19, No. 20 (1991) 5569-5574) which teaches MX is shown to react with AP sites produced in vivo after alkylation damage (pg 5569, right col, second full paragraph). Further, Examiner notes the instant claims are not directed at treating a specific cancer per se, but instead to potentiating the effect of an agent which induces the formation of AP sites. As such, where there is a known *in vitro* to *in vivo* correlation, it would be reasonable to expect the effect in cancerous cells would be similar to that demonstrated in the Chinese hamster ovary cells.

That said, Examiner previously noted the prior art teaches specifically that methoxamine increases the cytotoxicity of SN2 agents when tested in CHO cells (Fortini et al pg 91). Testing occurred in incubations that mimicked *in vivo* testing (*id.*). To further evidence the assay was acceptable in the art at the time of filing, Rosa et al (Nucleic Acids Research, Vol. 19, No. 20 (1991) 5569-5574) discusses MX is shown to react with AP sites produced in vivo after alkylation damage (pg 5569, right col, second full paragraph). Further, it is noted that the treatment of Chinese hamster cells treated with alkylating agent and MX showed improvement *in vivo* (pg 5572). Thus, the skilled artisan would find testing a single cell line with a single disclosed combination of drugs a

matter of routine testing where the predictability nature of the experiment is found in the *in vitro* testing, *in vivo* mimicking testing, and the recognition that testing cells with AP sites formed *in vivo* also produce the same desired effect. Thus, cancerous cells in the Chinese hamster ovaries would reasonably be expected have the same therapeutic effect when treated with the same agents used in the disclosed testing.

Finally, with regards to the teaching away of Fortini et al, Examiner acknowledges the prior art teaches the complexity of combining potetiating agents, but notes that the prior art specifically teaches the combination of SN2 agents with methoxamine. Thus, there does not appear to be teaching away appears to be limited to combinations of SN1 and methoxamine, but such combinations are not cited as part of the obviousness rejection. Instead, such teachings would direct the skilled artisan not to try SN1 agents, but focus on SN2 alkylating agents, which are within the scope of the instant claims.

Claim 238 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fortini et al (Carcinogenesis vol. 13 no. 1 (1992) pp.87-93) in view of Boulton et al (British J of Cancer (295) 72 849-856)).

Fortini et al is discussed above but does not disclose further administering a PARP inhibitor.

Boulton et al discloses temozolomide, an alkylating agent, is potentiated by administration of PARP inhibitors (pg 854 Discussion).

Boulton does not disclose further administration of methoxyamine.

It would have been obvious to one of ordinary skill in the art to combine two agents which are disclosed to potentiate the same active, an alkylating agent, in order to produce a third composition which would be expected to have a potentiated effect on the primary active agent.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-R 8-6 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612